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STUDY REPORT

DOUBLE-BLIND, RANDOMIZED, REPEATED DOSE, CROSSOVER COMPARISON OF
THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF CONTROLLED-
RELEASE OXYCODONE AND CONTROLLED-RELEASE MORPHINE IN CANCER
PATIENTS WITH PAIN

Sponsor

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Trial Exhibit

Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS);
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Average Daily Pain Intensity for The Last 3 Days of Double-Blind Period

	Period 1		Period 2		Combined	
	CR Oxy	CR Mor	CR Oxy	CR Mor	CR Oxy	CR Mor
Intent-to-Treat						
N	14	20	20	14	34	34
Mean	0.91	0.93	1.26	0.86	1.12*	0.90*
SE	0.14	0.13	0.16	0.13	0.11	0.09
Safety & Efficacy						
N	11	16	16	11	27	27
Mean	0.81	0.77	1.12	0.76	0.99**	0.77**
SE	0.16	0.11	0.16	0.11	0.12	0.07

*Significant treatment difference (p = 0.0044) and significant period effect (p = 0.0391).

**Significant treatment difference (p = 0.0048) and significant period effect (p = 0.0301).

Cross Reference: Tables 10.1A and 10.1C

The mean daily pain intensity ratings by time of day (overnight, morning, afternoon, and evening) for the last three days of the titration period and both double-blind periods are summarized below for the intent-to-treat population.

Three-day Mean Pain Intensity Ratings by Time of Day for all Periods Combined

Overnight	CR Oxycodone (=14)			Overnight	CR Morphine (=20)		
	Morning	Afternoon	Evening		Morning	Afternoon	Evening
0.99	1.01	1.31*	1.75*	0.78	0.86	1.10*	0.85*

*Significant treatment difference: afternoon (p=0.0398) and evening (p=0.0043)

Cross Reference: Table 10.2C

As shown, the mean pain scores remain in the range of slight pain (0.78 to 1.31). The pain ratings were fairly stable throughout the day with the afternoon pain rating slightly higher in both treatments. Small but statistically significant differences were noted between treatments for afternoon and evening ratings. These differences were considered minor and not clinically meaningful.

Pain Intensity Ratings at Blood Sampling Times

Pain intensity ratings on both the CAT scale and VAS are shown in Tables 12.2A and B for the safety and efficacy and intent-to-treat populations, respectively, for each timepoint on phlebotomy days when blood was drawn. The pain intensity ratings at each timepoint on the phlebotomy days in the intent-to-treat population for the combined periods are summarized below.

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Mean Pain Intensity Ratings at Time Of Phlebotomy

	CR Oxycodone (N=34)				CR Morphine (N=34)			
	0 Hour	1 Hour	3-4 Hours	5-6 Hours	0 Hour	1 Hour	3-4 Hours	5-6 Hours
VAS								
Mean	29.7	20.6	17.8	14.9	21.6	16.1	17.9	14.8
SE	4.2	3.2	3.4	2.6	3.4	3.4	3.5	3.2
CAT								
Mean	1.32	0.97	0.79	0.85	1.03	0.76	0.82	0.74
SE	0.15	0.12	0.13	0.10	0.13	0.13	0.12	0.11

Cross Reference: Table 12.2B

There were no significant differences in mean pain intensity by timepoint between treatments. Pain was well-controlled on both treatments and decreased after dosing.

Time to Achieve Stable Dosing

The time to achieve stable dosing was defined as the total number of titration days required to attain a stable dose which produced good daily pain control (mean ≤ 1.25 on CAT) and required minimal (≤ 2 doses) rescue. A summary of successful titration and the days required to attain a stable dose using either CR oxycodone or CR morphine is shown below.

Patients Titrated to a Stable Dose

	CR Oxycodone (n = 23)		CR Morphine (n = 22)		Total (n = 45)	
	n	(%)	n	%	n	%
Titration						
Successful	16	(70)	18	(82)	34	(78)
Unsuccessful	7	(30)	4	(18)	11	(24)
Days to Stable Pain						
0	8	(35)	9	(41)	17	(38)
1-2	3	(13)	6	(27)	9	(20)
3-4	2	(9)	1	(5)	3	(7)
> 4	3	(13)	2	(9)	5	(11)
Median ^a	3.0		1.5			

^aMedian derived using product-limit estimation.

Cross Reference: Table 6

Seventy percent of patients treated with CR Oxycodone and 82% of those treated with CR morphine were titrated to stable pain management. Thirty-eight percent of the total patients converted directly without need for titration or dose adjustment; 85% of those successfully titrated reached a stable dose by the fourth day of dosing. The median time to stable dosing was 3 days for CR oxycodone and 1.5 days for CR morphine. There were no significant difference in the time to achieve stable pain control.

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Mean Number of Rescue Doses during Double-Blind Periods

The mean number of rescue doses taken during the last three days of the double-blind periods of the study and the average over the last three days are shown for the intent-to-treat population that completed both periods (Table 8.1B) and for the safety and efficacy population (Table 8.1A). In both populations the mean number of rescue doses was approximately 1 to 1.5 doses per day and never exceeded two on any day or in either period, thus overall the daily number of rescue doses was within the limits established during titration by the definition of stable pain.

In the combination of both periods in the intent-to-treat population (Table 8.1B), the mean number of rescue doses taken by the patients treated with CR oxycodone was significantly higher than the mean number taken by the patients treated with CR morphine on Days 1 and 2 and over the three-day average. The results are summarized below.

**Mean Rescue Doses during Last Three Days of the
Combined Double-Blind Periods**

	Intent-to-Treat (Total Patients=34) ^a	
	CR Oxycodone	CR Morphine
Day 3	1.32	0.88
Day 2	1.59*	0.88*
Day 1	1.62*	0.79*
3-Day Average	1.51*	0.85*

^aTwo patients discontinued in Period 1 excluded

*Significant treatment differences: Day 1 ($p = 0.0015$), Day 2 ($p = 0.0066$), and 3-day average ($p = 0.0013$)

Cross Reference: Table 8.1B

Number of Dose Adjustments During Titration

Patients were titrated to stable pain with daily doses of either CR oxycodone or CR morphine. The goal of titration was an acceptable level of pain relief without unacceptable adverse events and, most commonly, was considered a score of none or slight on the CAT scale with no more than two rescue doses a day and the maintenance of a stable total daily dose for at least 48 hours. The number of patients who required upward dose adjustments to achieve stable pain control with CR oxycodone or CR morphine during titration is shown below along with the totals of both treatment groups. Also shown are the number of patients titrated and the mean and median number of adjustments required in each group.

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8.0 CONCLUSIONS

8.1 Protocol and Adherence to Protocol

This study was a double-blind, repeated dose, crossover trial of CR oxycodone which is being studied under an IND exemption (# ?), compared with CR morphine, an approved product. The subject population included patients with chronic cancer pain, and the study was conducted at one recruited center in Finland.

This clinical trial was conducted in accordance with the Principles of the Declaration of Helsinki. Purdue Pharma L.P. maintains and follows standard operating procedures which codify procedures. Frequent site monitoring and other types of data validation allow confidence that the data contained in this report are correct.

8.2 Efficacy

This study enrolled 45 chronic cancer pain patients into titration with 36 of these patients going on to the double-blind, crossover comparison. At baseline, prior to titration, patients were in moderate to severe pain with an acceptability of therapy that was fair to poor. In the titration period there were no significant differences between the CR oxycodone and CR morphine treatment groups with respect to the number of days required to achieve stable pain control, and the number of patients who reached, stable pain control was similar in the two treatment groups. Approximately 48% of the CR oxycodone patients and 55% of the CR morphine patients required either no titration or only one dose adjustment, which occurred within a day of initiation of titration (Table 5). The rapidity with which stable pain control was attained together with the large percentage of patients requiring no or very brief titration contrasts with the generally recognized need to titrate the vast majority of opioid analgesics in the management of most cancer patients. These data confirm the appropriateness of the conversion guidelines utilized in this study, and also demonstrate consistency in therapeutics from patient to patient with the use of oral oxycodone.

There were some statistically significant differences between treatment groups and periods for pain intensity and acceptability of therapy ratings. However, differences between treatment groups at baseline and over the last three days of each period were minor and appear to have no clinical significance; pain was at all times controlled at slight levels and ratings of acceptability of therapy were all between fair and good.

The pain intensity ratings were examined for differences between younger (< 65 years of age) and older (≥ 65) patients and between men and women. Differences between younger and older patients were not significant during any part of the study; women at baseline, but not during titration, had significantly lower pain ratings over the past 24 hours, compared to men. During the double-blind part of the study, a significant treatment by sex interaction was seen. Treatment differences for men were not significant, but women (n = 12 out of 34) had significantly less pain with CR morphine, compared with CR oxycodone, over the last three days of the study. Women also had better acceptability of therapy over the three-day average when treated with CR morphine (3.41 with CR morphine, compared with 3.13 in the CR oxycodone group).

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The average number of rescue doses was higher for patients who were treated with CR oxycodone than with CR morphine (1.51 vs 0.85 in the intent-to-treat population over the three-day average).

During the pharmacokinetic study, the adjusted plasma oxycodone concentrations at 0, 3 to 4 and 5 to 6 hours, post-dose were significantly higher than those of morphine in the intent-to-treat population. In general, as plasma oxycodone and morphine concentrations increased, pain intensity ratings decreased and were maintained at a slight pain level (Figures A and B).

8.3 Safety

Safety was evaluated during two distinct parts of the study: titration and the double-blind periods. Safety was assessed by evaluating dropouts because of adverse events and by incidence of adverse events. Changes in vital signs were monitored. In the titration and double-blind parts of the study, typical, common opioid side effects were observed and included nausea, vomiting, constipation, dizziness, somnolence and pruritus. In general, patients in both the CR Oxycodone and CR morphine groups experienced these adverse events, and differences between treatments were not significant.

Review of vital signs revealed no clinically significant changes in pulse, respiratory rate, temperature and blood pressures in patients on CR oxycodone or CR morphine.

8.4 Risk/Benefit

The risks of CR oxycodone and CR morphine tablets are equivalent to those of their IR counterparts, which are well-known and have been established in previous protocols. Morphine was first isolated from opium in 1806, and use of the purified preparation has been widespread since the middle of the 19th century. Oxycodone has been in human use since 1917, and IR oxycodone tablets are marketed in the USA. The CR dosage forms add no additional risk and may actually reduce the risk because of a slower absorption.

Although at certain times and days in the double-blind part of the study, pain intensity ratings with CR morphine were statistically lower than with CR oxycodone, both CR oxycodone and CR morphine controlled pain effectively. Clinically, it was difficult to distinguish between CR morphine and CR oxycodone as analgesics. In that regard, it should be remembered that in the last three days of the double-blind periods and over the three-day average, the pain mean intensity ratings never exceeded 1.25 although on phlebotomy days the mean pain intensity rating with CR oxycodone prior to dosing (zero hour) in the combined double-blind periods was 1.32. This single timepoint was the only one at which the average pain rating exceeded 1.25.

In conclusion, this study demonstrates that CR oxycodone provides cancer patients with effective pain control essentially equivalent to that with CR morphine. Furthermore, CR oxycodone has a favorable safety profile that is similar to that of CR morphine. Therefore, the efficacy and safety of CR oxycodone make it a good choice for the control of pain in cancer patients.

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